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CASE REPORT

Asymptomatic Propylthiouracil Induced Agranulocytosis in a Patient with Toxic Nodular Goiter: A Rare Case Report

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Background: Agranulocytosis is a rare but fatal side effect of antithyroid drugs (ATDs) with incidence reported at 0.1%-1%. Agranulocytosis is defined as a granulocyte count <500 cells/μL following the use of ATDs and is an absolute contraindication to the use of these drugs; in this case, radioactive iodine (RAI) or surgery are therapeutic options.

Case Presentation: A 28-year-old female patient was on follow-up at our clinic after she presented with anterior neck swelling of 4 years. The patient was started on propylthiouracil (PTU) and propranolol based on clinical symptoms of hyperthyroidism and low thyroid stimulating hormone (TSH) levels. After taking the ATDs for 7 months, she came to the clinic for her regular follow-up. At this point, she was declared euthyroid and booked for surgery. Investigations were sent and the complete blood count (CBC) result showed leucopenia with agranulocytosis, even though she was completely asymptomatic. The offending ATD was immediately discontinued. The patient was kept inpatient for monitoring, and lugol's iodine and propranolol were initiated. Eight days after discontinuing the ATD, the CBC profile was determined once again, showing normalized total leukocyte, as well as, absolute neutrophil count. Eventually, the multinodular goiter (MNG) was managed with subtotal thyroidectomy.

Conclusion: Despite the fact that agranulocytosis is an extremely rare side effect of ATDs, most often PTU; it is a potentially fatal complication when it occurs. Patient education at the time of prescription should not be overlooked, and systematic programs should be put in place. The baseline granulocyte count should be determined and monitored on a regular basis.

Keywords: antithyroid drugs, ATDs, PTU-induced agranulocytosis, drug-induced agranulocytosis, G-CSF, case report

Introduction

One of the numerous causes of an enlarged thyroid gland is toxic multinodular goiter (MNG). Multiple autonomously functioning nodules in the enlarged thyroid gland produce excessive amounts of thyroid hormone independent of stimulation by thyroid stimulating hormone (TSH), which causes hyperthyroidism. Anti-thyroid drugs (ATDs) must be used to render patients euthyroid before either radioactive iodine ablation or more frequently, surgery is used to treat the condition definitely. Older women are more commonly affected. A cross-sectional study from Tikur Anbessa Specialized Hospital showed that the majority of the patients with toxic goiter had toxic multinodular goiter, accounting for 35.9% of the cases followed by Graves' disease (17.3%). Ninety percent of the patients were female, and age 40 and above accounted for 59% of the cases. Thyrotoxicosis was treated with Propylthiouracil 96.8% of the time with or without beta blockers. Most of these nodules are benign; however, on occasion, they may harbor malignancy.[1]

The thyroid peroxidase (TPO) enzyme, which affects multiple steps in the synthesis of thyroid hormone, is inhibited by thioamide ATDs. The typically prescribed drugs are methimazole and propylthiouracil (PTU). PTU also inhibits the conversion of T4 to T3 in peripheral tissues.[2,3] Despite the fact that methimazole (Tapazole) or carbimazole (except in the first trimester of pregnancy) are preferable first-line treatments due to a lower risk of life-threatening adverse effects

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such as severe hepatotoxicity when compared to PTU, due to the issue of availability and accessibility, in Jimma, PTU is the most frequently administered ATD for hyperthyroidism of any underlying cause.

PTU is a common therapeutic choice for hyperthyroidism treatment, especially if methimazole or radioactive iodine treatment is contraindicated or as an alternative treatment option in a patient with Graves' disease or toxic multinodular goiter.[4] It is used before thyroidectomy or radioactive iodine therapy to treat hyperthyroidism. It is also indicated in thyroid storm and thyrotoxicosis crisis. It is a preferred antithyroid drug in the first trimester of pregnancy. Agranulocytosis is one of the adverse effects of PTU which is potentially life-threatening and occurs in 0.2 to 0.5% of patients. The patients should receive instruction to report any symptoms suggestive of pancytopenia – fever, sore throat, interstitial pneumonitis. The risk is at its highest in the first three months of treatment. Other major adverse effects include acute liver failure (for which PTU has a black box warning), hypothyroidism, ANCA associated vasculitis, hypersensitivity reaction (Steven Johnson syndrome, toxic epidermal necrolysis, and urticaria).[4,5] Mild and more prevalent side effects are fever, arthralgias, and lymphadenopathy. Cholestatic jaundice, lupus-like syndrome, hypergammaglobulinemia, taste and smell abnormalities, sialadenitis, myopathy, and hair loss are less frequent side effects.[6] There is not a clear dose relationship for propylthiouracil (PTU) related adverse effects.[7]

A granulocyte count of below 500 cells/L after using ATDs is defined as agranulocytosis.[8] Due to the potential cross-reactivity, thioamides should never be used on individuals who have already developed agranulocytosis. In this condition, the only available treatments are radioactive iodine ablation (RAI) or surgery.[9] Here, we describe a 28-year-old female patient with toxic MNG who, seven months into receiving PTU treatment, developed severe agranulocytosis. The article was reported in accordance with SCARE criteria.[10]

Case Presentation

A 28-year-old female patient was on follow-up at our clinic after she presented with anterior neck swelling of 4 years. She claimed that the swelling was small at the beginning but progressed in size gradually, at which time she started filling some pressure locally. Lately, she had also been feeling easily fatigued, she has had palpitation and shortness of breath on exertion, and some degree of heat intolerance. However, her appetite had been as usual and she did not experience any weight loss. Upon examining her, her blood pressure was 118/80 mmHg, pulse rate was 114 beats per minute, and the temperature was 36.6°C. Neck examination showed 5cm × 6cm measuring enlarged thyroid gland in the anterior neck, which had firm consistency, nodular surface with mobility and no tenderness. There were no clinically detectable cervical lymphadenopathies (LAP). There were no signs of ophthalmopathy, and neurologic exam was normal. During her initial diagnosis, she was investigated with baseline complete blood count (CBC) (Table 1), serum TSH, T3 and T4, liver function tests (LFT), neck ultrasound and fine needle aspiration cytology (FNAC).

Despite having normal free T3 and T4 levels, the patient was started on PTU 100 mg orally three times daily (TID) and propranolol 40 mg PO TID based on clinical symptoms of hyperthyroidism and low TSH levels. Neck ultrasound revealed that both thyroid lobes were enlarged in size due to multiple heterogeneous echo benign nodules with internal coarse shadowing calcifications, largest in the right lobe measuring 3.5 × 2.5 cm in the widest dimension. There were no significant LAP (Figure 1). Thyroid scintigraphy is warranted in this case, however due to its unavailability in our setting, we could not perform it. On FNAC, smear showed low cellular yield composed of sheets and clusters of atypical cyst lining cells, lymphocytes and abundant thin and thick colloid in fluidy background. The conclusion was atypia of undetermined significance (AUS); therefore, repeat FNAC after 3 months was planned. The repeat FNAC showed moderate cellular yield composed of clusters and dispersed bland follicular epithelial cells, along with foamy histiocytes, cyst lining cells and abundant thin and thick colloid in fluidy background. The index was nodular colloid goiter with hyperplastic focus.

After taking the ATDs for 7 months, she came to the clinic for her regular follow-up, at which point she was experiencing none of the clinical features of hyperthyroidism. Her pulse rate was maintained within the normal limits (80–84 beats per minute) and the TSH, T3 and T4 had normalized (Table 2).

At this point, the patient was advised to have a definitive thyroidectomy to treat the toxic MNG and was admitted to the elective surgical department. Upon admission routine pre-operative lab investigations were sent. The LFT was within normal limits and the CBC test done twice 24 hours apart showed leucopenia with agranulocytosis (Table 3 and Table 4).

Table 1 Initial Laboratory Tests at the Clinic

Date: 08/08/22			**Reference Range**
WBC	4.41	[10^3/μL]	3.00–15.00
RBC	5.29	[10^6/ μL]	2.50–5.50
HGB	15.7	[g/dl]	8.0–17.0
HCT	46.9	[%]	26.0–50.0
MCV	88.7	[FL]	86.0–110.0
MCH	29.7	[Pg]	26.0–36.0
MCHC	33.5	[g/dl]	31.0–37.0
PLT	199	[10^3/μL]	150–450
RDW-SD	45.0	[FL]	37.0–54.0
RDW-CV	14	%	11.0–16.0
PDW	11.8	[FL]	9.0–17.0
MPV	10.6	[FL]	9.0–13.0
P-LCR	28.7	[%]	13.0–43.0
PCT	0.21	[%]	0.17–1.35
NEUT	2.2	[10^3/μL]	1.50–7.0
LYMPH	1.8	[10^3/μL]	1.0–3.7
MONO	0.2	[10^3/μL]	0.0–0.7
EO	0.1	[10^3/μL]	0.00–0.40
Lab Test	**Values**		**Reference Range**
TSH	0.11μIU/mL		0.3–4.5
FreeT3	14.9pg/mL		8.9–17.2
Free T4	2.17pg/mL		2.0–4.2

Abbreviations: WBC, White blood cell count; RBC, Red blood cell count; HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean corpuscular volume; Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; PLT, Platelets; RDW-SD, Red cell distribution width (standard deviation); RDW- CV, Red cell distribution width in percent; PDW, Platelet distribution width; MPV, Mean platelet volume; P-LCR, Platelet- large cell ratio; PCT, Plateletcrit; NEUT, Neutrophil; LYMPH, Lymphocyte; MONO, Monocyte; EO, Eosinophil; TSH, Thyroid stimulating hormone; T3, Triiodothyronine; T4, Tetraiodothyronine.

The patient had no fever, sore throat or any other signs and symptoms of infection, and the agranulocytosis was an incidental finding.

The diagnosis of asymptomatic PTU-induced agranulocytosis was made, with absolute neutrophil count of less than 500/μL, while she was on PTU for the control of hyperthyroidism which was not evident on her initial CBC profiles. Since she was asymptomatic and work-up for infection (urine analysis and chest X-ray) were unremarkable, she was not started on broad-spectrum antibiotics. However, the offending ATD was immediately discontinued. The patient was kept inpatient for monitoring on lugol's iodine and propranolol 20 mg po QID. She was advised on danger signs like sore throat, fever, cough and so on. Eight days after discontinuing the ATD, the CBC profile was determined once again, showing normalized total leukocyte, as well as, absolute neutrophil count (Table 5).

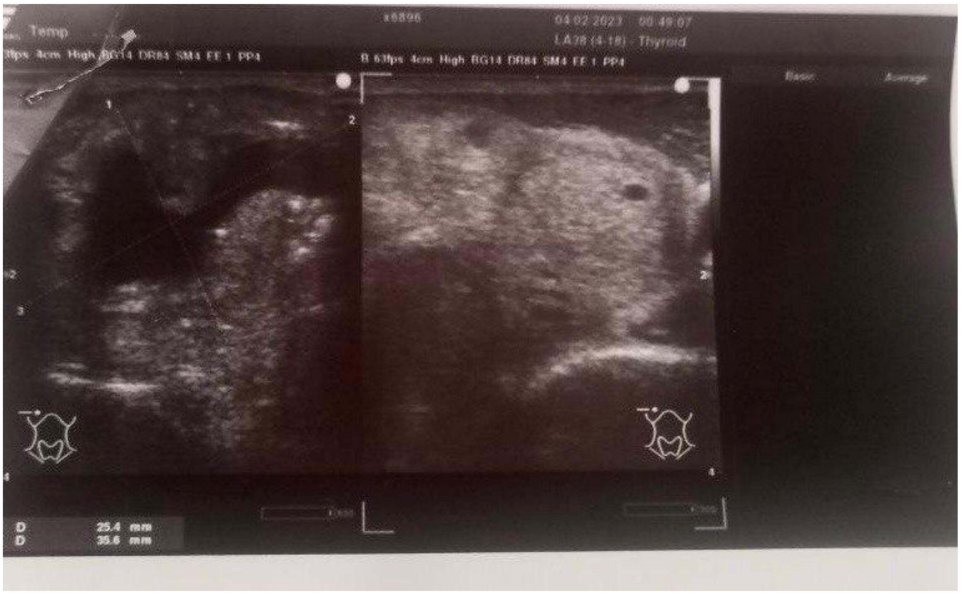

Figure 1 Multiple heterogeneous echo benign nodules with internal coarse shadowing calcifications.

After informed consent was obtained from the patient, she was taken to the operation theater. She was put under general anesthesia, and subtotal thyroidectomy was performed. The intra-operative finding was 8 × 6 cm measuring thyroid gland with multiple calcified nodules (Figure 2).

Dunhill's thyroidectomy procedure was performed after identifying and preserving both RLNs and the parathyroid glands. Drainage was left in the thyroid bed and incision closed in layers. The patient had smooth post-operative course, and she got discharged on the 2nd post-op day (POD). Histopathological analysis revealed nodular colloid goiter with cystic degeneration (Figure 3). The patient was followed for 6 months at the outpatient clinic. She has no complaints, and her clinical examination and laboratory test results are normal. She is clinically, as well as biochemically, euthyroid.

Discussion

A multi-nodular goiter with symptoms of hyperthyroidism is toxic multi-nodular goiter (MNG). A few of the nodules had become autonomous over time, causing hyperthyroidism that ranges from subclinical to severe thyrotoxicosis. It is the second most frequent cause of thyrotoxicosis worldwide, behind Graves' disease. However, it is more prevalent in iodine deficient areas like ours. The TSH receptor (TSHR) gene's somatic point mutations are what cause the TSH receptor to activate independently of TSH.[11] Signs and symptoms of hyperthyroidism are frequently observed in patients. First-line diagnostic modalities include laboratory tests (serum TSH, T3 and T4 levels), imaging studies (neck ultrasound, thyroid scintigraphy) and fine needle aspiration biopsy (FNAB).

Table 2 Serum Thyroid Function Test After 7 Months of ATDS

Lab Test	Results	Reference Range
TSH	1.277μIU/mL	0.35–4.94
Free T3	2.57 pg/mL	1.58–3.91
Free T4	1.01 ng/dl	0.70–1.48

Abbreviations: TSH, Thyroid stimulating hormone; T3, Triiodothyronine; T4, Tetraiodothyronine.

Table 3 CBC Profile of the Patient Upon Admission

2023/03/05			Reference Range
WBC	1.48	[10^3/μL]	3.00–15.00
RBC	4.50	[10^6/ μL]	2.50–5.50
HGB	13.7	[g/dl]	8.0–17.0
HCT	41.1	[%]	26.0–50.0
MCV	91.3	[FL]	86.0–110.0
MCH	30.4	[Pg]	26.0–36.0
MCHC	33.3	[g/dl]	31.0–37.0
PLT	253	[10^3/μL]	150–450
RDW-SD	44.2	[FL]	37.0–54.0
RDW-CV	13.6	%	11.0–16.0
PDW	11.0	[FL]	9.0–17.0
MPV	9.8	[FL]	9.0–13.0
P-LCR	23.0	[%]	13.0–43.0
PCT	0.25	[%]	0.17–1.35
NEUT	0.57(39.0%)	[10^3/μL]	1.50–7.0
LYMPH	0.01(0.7%)	[10^3/μL]	1.0–3.7
MONO	0.86(58.9%)	[10^3/μL]	0.0–0.7
EO	0.01(0.7%)	[10^3/μL]	0.00–0.40
BASO	0.01(0.7%)	[10^3/μL]	0.00–0.10

Abbreviations: WBC, White blood cell count; RBC, Red blood cell count; HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean corpuscular volume; Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; PLT, Platelets; RDW-SD, Red cell distribution width (standard deviation); RDW- CV, Red cell distribution width in percent; PDW, Platelet distribution width; MPV, Mean platelet volume; P-LCR, Platelet- large cell ratio; PCT, Plateletcrit; NEUT, Neutrophil; LYMPH, Lymphocyte; MONO, Monocyte; EO, Eosinophil; BASO, Basophil.

Surgery is the most appropriate treatment option for toxic MNG. The extent of the disease will determine whether total, nearly total, or subtotal thyroidectomy is necessary. To optimize patients for surgery, ATDs such as propylthiouracil, carbimazole, and its active metabolite methimazole are employed.[12] PTU is preferred over methimazole during the first trimester of pregnancy. With the exception of pregnancy, hyperthyroidism can be safely controlled with carbimazole or methimazole.[13]

According to recommendations from the American Thyroid Association (ATA) and American Association of Clinical Endocrinology (AACE), when serum TSH is less than 0.1 mIU/L, people with subclinical hyperthyroidism should be treated. These recommendations also apply to postmenopausal women who are not taking estrogen or bisphosphonates as well as to people with hyperthyroid symptoms. Additionally, those over 65 with or without hyperthyroid symptoms and whose serum TSH levels consistently remain below 0.1 mU/L should start receiving treatment.[14] It was decided to treat our patient since she complained of pressure symptoms caused by the mass, had hyperthyroidism symptoms, tachycardia and a serum TSH level that was just slightly above 0.1 mIU/L. Even though she was started on antithyroid drugs to optimize her for surgery, the dose and the duration of treatment is not justified.

Table 4 Repeat CBC Profile the Next Day

2023/03/06			Reference Range
WBC	1.50	[10^3/μL]	3.00–15.00
RBC	4.38	[10^6/ μL]	2.50–5.50
HGB	13.9	[g/dl]	8.0–17.0
HCT	42.1	[%]	26.0–50.0
MCV	95.9	[FL]	86.0–110.0
MCH	31.8	[Pg]	26.0–36.0
MCHC	33.1	[g/dl]	31.0–37.0
PLT	245	[10^3/μL]	150–450
RDW-SD	47.2	[FL]	37.0–54.0
RDW-CV	14.4	%	11.0–16.0
PDW	10.0	[FL]	9.0–17.0
MPV	9.8	[FL]	9.0–13.0
P-LCR	24.6	[%]	13.0–43.0
PCT	0.244	[%]	0.17–1.35
NEUT	0.49(32.6%)	[10^3/μL]	1.50–7.0
LYMPH	0.01(0.7%)	[10^3/μL]	1.0–3.7
MONO	0.86(58.9%)	[10^3/μL]	0.0–0.7
EO	0.01(0.7%)	[10^3/μL]	0.00–0.40

Abbreviations: WBC, White blood cell count; RBC, Red blood cell count; HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean corpuscular volume; Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; PLT, Platelets; RDW-SD, Red cell distribution width (standard deviation); RDW- CV, Red cell distribution width in percent; PDW, Platelet distribution width; MPV, Mean platelet volume; P-LCR, Platelet- large cell ratio; PCT, Plateletcrit; NEUT, Neutrophil; LYMPH, Lymphocyte; MONO, Monocyte; EO, Eosinophil.

Antithyroid medications do have certain adverse reactions although being generally safe. A patient's chance of experiencing milder side effects, which are more frequently related to PTU therapy, ranges from 3 to 12%.[7] Agranulocytosis, a less common but potentially fatal side effect of thioamide therapy, typically develops within the first three months of treatment and has a prevalence of 0.1% to 0.5%.[15] The patient in this example was asymptomatic, but she developed agranulocytosis as a side effect 7 months after starting the medication.

In 1952, Bartels and Sjogren reported the first instance of ATD-induced agranulocytosis.[16] In 1952, a patient receiving methimazole experienced severe bilateral pneumonia and succumbed to it, which was the first mortality related to ATD treatment.[17] Absolute neutrophil count (ANC) below 500/l of blood has been identified as a marker for drug-induced agranulocytosis.[18] In actuality, most patients have an ANC below 100/l.[19] According to Bénichou and Solal-Celigny, the following three criteria can be used. The following conditions must be met: (1) onset of agranulocytosis during therapy or within seven days of discontinuation of the medication; (2) full recovery with ANC > 1500/l within one month of medication discontinuation; (3) Ruling out of congenital neutropenia or immune neutropenia and recent infectious disease.[20] In the largest published series of ATD-induced agranulocytosis, females were 6 times more likely to be affected than males. Furthermore, elderly individuals were more frequently affected.[21]

Table 5 Normalized CBC Profile After Discontinuation of PTU

2023/03/15			Reference Range
WBC	4.72	[10^3/μL]	3.00–15.00
RBC	4.41	[10^6/ μL]	2.50–5.50
HGB	13.6	[g/dl]	8.0–17.0
HCT	40.1	[%]	26.0–50.0
MCV	90.9	[FL]	86.0–110.0
MCH	30.8	[Pg]	26.0–36.0
MCHC	33.9	[g/dl]	31.0–37.0
PLT	269	[10^3/μL]	150–450
RDW-SD	44.9	[FL]	37.0–54.0
RDW-CV	13.8	%	11.0–16.0
PDW	11.3	[FL]	9.0–17.0
MPV	10.1	[FL]	9.0–13.0
P-LCR	25.2	[%]	13.0–43.0
PCT	0.27	[%]	0.17–1.35
NEUT	2.10(44.6%)	[10^3/μL]	1.50–7.0
LYMPH	1.96(41.5%)	[10^3/μL]	1.0–3.7
MONO	0.54(11.4%)	[10^3/μL]	0.0–0.7
EO	0.11(2.3%)	[10^3/μL]	0.00–0.40
BASO	0.01(0.2%)	[10^3/μL]	0.00–0.10

Abbreviations: WBC, White blood cell count; RBC, Red blood cell count; HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean corpuscular volume; Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; PLT, Platelets; RDW-SD, Red cell distribution width (standard deviation); RDW- CV, Red cell distribution width in percent; PDW, Platelet distribution width; MPV, Mean platelet volume; P-LCR, Platelet- large cell ratio; PCT, Plateletcrit; NEUT, Neutrophil; LYMPH, Lymphocyte; MONO, Monocyte; EO, Eosinophil; BASO, Basophil.

The exact pathophysiology is unknown, but some theories put forth include the oxidation of the drug by neutrophils into reactive metabolites, activating inflammasomes, and an immune-mediated process where circulating antibodies against differentiated granulocytes cause apoptosis. Through the complement system, these antibodies can also interact with myeloid progenitor cells and trigger neutrophil opsonization.[19,22–24] Although cases have been documented as early as five days and as late as ten years, agranulocytosis frequently manifests within the first three months of commencing ATD treatment.[24] The average number of days for various thioamide medications to cause agranulocytosis was found to be between 36 and 42 days.[25–27] Fever and a sore throat are the most common symptoms. Acute pharyngitis is the most typical source of infection, but pneumonia and anorectal infections may also arise.[28] As in our case, 15% of people may be asymptomatic.[24] Nevertheless, they could develop symptoms soon after getting a diagnosis. High doses, sporadic use, and older age can be highly associated with its occurrence.[29] Although it is extremely uncommon, when it does happen, there is a 2–10% mortality risk. Poor prognosis is mainly related to age >65, pancytopenia, liver impairment, and renal failure.[30,31]

The patient should be instructed to seek health care once a fever or sore throat appears after therapy has begun.[32] The leukocyte count should also be kept track of. The offending antithyroid drugs should be withdrawn when the leukocyte

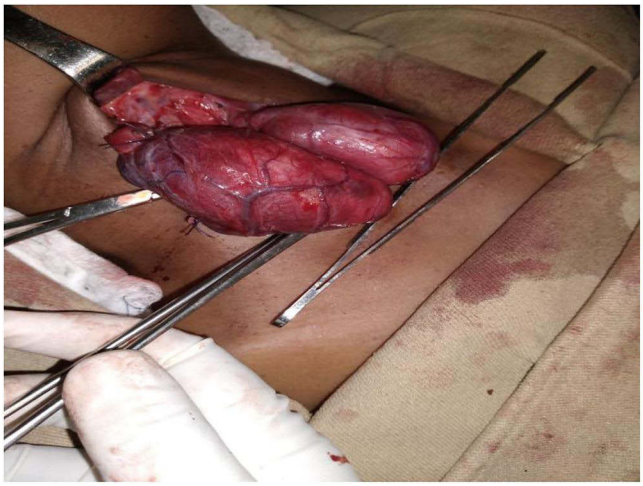

Figure 2 Bilateral nodular, calcified, colloid goiter.

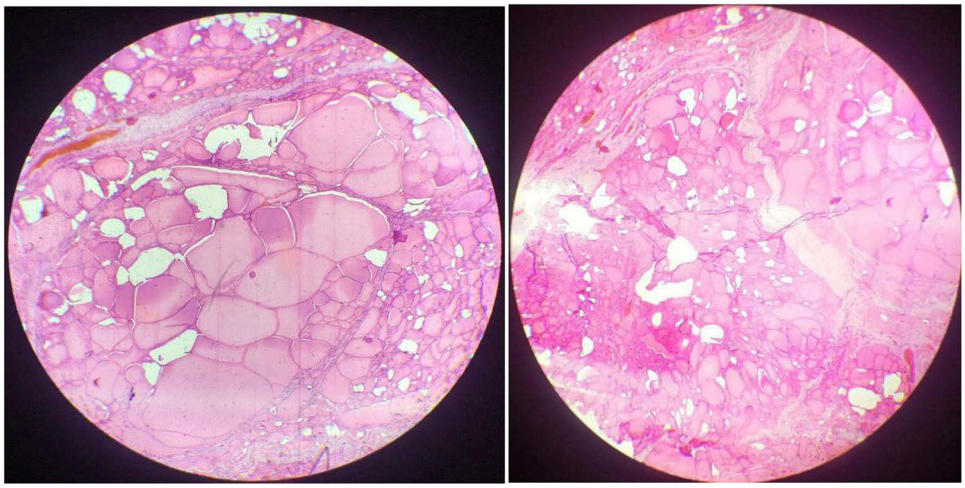

Figure 3 Irregularly enlarged follicles with flattened epithelium; multinodular goiter.

count drops to less than 1500/l.[33] As soon as possible, patients should be admitted to the hospital for observation and IV antibiotics administration. Broad-spectrum intravenous antibiotics should be given as soon as blood, urine, and other sample cultures are completed. It is recommended to take preventative steps, such as practicing excellent hygiene in high-risk regions like the mouth, skin, and perineum.[19] Hematopoietic growth factors, like granulocyte-colony stimulation factors (G-CSFs), may be used to treat agranulocytosis brought on by ATD. The use of G-CSF has been shown to speed up hematological recovery, shorten the course of antibiotic therapy, reduce hospital stays, and reduce overall expenditures.[34,35] Because G-CSF is not available in our set-up, the patient was not given any.

Because a cross-reaction between carbimazole and propylthiouracil was identified in 15.2% of patients,[36] alternative treatments for hyperthyroidism should be provided. In order to restore euthyroidism, surgery or radioactive iodine seem to be reasonable options. Since surgery is a more effective definitive treatment for controlled toxic MNG, our patient was treated surgically once her granulocyte count returned to normal.

Conclusion

Despite the fact that agranulocytosis is an extremely rare side effect of ATDs (especially PTU), it is a potentially fatal complication when it occurs. Patient education at the time of prescription should not be overlooked, and systematic

programs should be put in place. Pharmacological treatment for subclinical hyperthyroidism should only be offered selectively. If treatment is indicated, the baseline granulocyte count should be determined and monitored on a regular basis.

Ethics

Case reports are exempt from ethical approval by the institutional review board of Jimma University as long as written informed consent is obtained from the patient and identifying details are removed.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. We confirm that identifying details were not included in the manuscript.

Acknowledgments

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing, we confirm that we have followed the regulations of our institutions concerning intellectual property.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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